

IN THE CLAIMS:

Please cancel claims 437 to 480 without prejudice or disclaimer and add new claims 481 to 556 as shown below.

1-432. (Previously cancelled)

437-480. (Currently cancelled)

433. (Previously added) A method of binding oligonucleotides to nanoparticles to produce stable nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides having covalently bound thereto a moiety comprising a functional group which can bind to the nanoparticles;

contacting the oligonucleotides and the nanoparticles in aqueous solution for a period of time sufficient to allow at least some of the oligonucleotides to bind to the nanoparticles;

adding at least one salt to the aqueous solution to form a salt solution; and

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow sufficient additional oligonucleotides to bind to the nanoparticles to produce the stable nanoparticle-oligonucleotide conjugates.

434. (Previously added) The method of Claim 433 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

435. (Previously added) The method of Claim 434 wherein the nanoparticles are gold nanoparticles.

436. (Previously added) The method of Claim 435 wherein the moiety comprising a functional group which can bind to the nanoparticles is an alkanethiol.

481. (New) The method of Claim 433 wherein the oligonucleotides are bound to the nanoparticles through sulfur linkages.

482. (New) The method of Claim 433 wherein the oligonucleotides and nanoparticles are contacted in aqueous solution for about 12 to about 24 hours.

483. (New) The method of Claim 433 wherein salt is added to the aqueous solution to form the aqueous salt solution that is buffered at pH 7.0 and that contains about 0.1 M NaCl.

484. (New) The method of Claim 433 wherein the oligonucleotides and nanoparticles are contacted in the salt solution for an additional 40 hours to increase the density of oligonucleotides bound to the nanoparticles.

485. (New) The method of Claim 433 wherein the salt is added to the aqueous solution in a single addition.

486. (New) The method of Claim 433 wherein the salt is added gradually to the aqueous solution over time.

487. (New) The method of Claim 433 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

488. (New) The method of Claim 433 wherein the salt is sodium chloride in a phosphate buffer.

489. (New) The method of Claim 433 wherein nanoparticle-oligonucleotide conjugates are produced having the oligonucleotides present on a surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

490. (New) The method of Claim 489 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

491. (New) The method of Claim 490 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

492. (New) A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides, the oligonucleotides comprising at least one type of recognition oligonucleotides, each of the recognition oligonucleotides comprising a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles; and

contacting the oligonucleotides and the nanoparticles under conditions effective to allow at least some of the recognition oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

493. (New) The method of Claim 492 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

494. (New) The method of Claim 492 wherein the oligonucleotides are bound to the nanoparticles through sulfur linkages.

495. (New) The method of Claim 492 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

496. (New) The method of Claim 495 wherein the nanoparticles are gold nanoparticles.

497. (New) The method of Claim 492 wherein the spacer portion comprises at least about 10 nucleotides.

498. (New) The method of Claim 497 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

499. (New) The method of Claim 498 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils, or all guanines.

500. (New) The method of Claim 492 wherein the effective conditions comprise contacting the oligonucleotides and the nanoparticles in aqueous solution for a period of time sufficient to allow at least some of the oligonucleotides to bind to the nanoparticles;

adding at least one salt to the aqueous solution to form a salt solution; and
contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow sufficient additional oligonucleotides to bind to the nanoparticles to produce the stable nanoparticle-oligonucleotide conjugates.

501. (New) The method of Claim 500 wherein the oligonucleotides and nanoparticles are contacted in aqueous solution for about 12 to about 24 hours.

502. (New) The method of Claim 500 wherein salt is added to the aqueous solution to form the aqueous salt solution that is buffered at pH 7.0 and that contains about 0.1 M NaCl.

503. (New) The method of Claim 500 wherein the oligonucleotides and nanoparticles are contacted in the salt solution for an additional 40 hours to increase the density of oligonucleotides bound to the nanoparticles.

504. (New) The method of Claim 500 wherein the salt is added to the aqueous solution in a single addition.

505. (New) The method of Claim 500 wherein the salt is added gradually to the aqueous solution over time.

506. (New) The method of Claim 500 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

507. (New) The method of Claim 500 wherein the salt is sodium chloride in a phosphate buffer.

508. (New) The method of Claim 500 wherein nanoparticle-oligonucleotide conjugates are produced having the oligonucleotides present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

509. (New) The method of Claim 508 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

510. (New) The method of Claim 509 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

511. (New) A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles under conditions effective to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

512. (New) The method of Claim 511 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

513. (New) The method of Claim 512 wherein the nanoparticles are gold nanoparticles.

514. (New) The method of Claim 511 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles.

515. (New) The method of Claim 511 wherein the oligonucleotides are bound to the nanoparticles through sulfur linkages.

516. (New) The method of Claim 514 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

517. (New) The method of Claim 514 wherein the spacer portions of the recognition oligonucleotides comprises at least about 10 nucleotides.

518. (New) The method of Claim 517 wherein the spacer portions of the recognition oligonucleotides comprises from about 10 nucleotides to about 30 nucleotides.

519. (New) The method of Claim 514 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils or all guanines.

520. (New) The method of Claim 514 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

521. (New) The method of Claim 520 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

522. (New) The method of Claim 511 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

523. (New) The method of Claim 511 wherein the effective conditions comprise contacting the oligonucleotides and the nanoparticles in aqueous solution for a period of time sufficient to allow at least some of the oligonucleotides to bind to the nanoparticles;

adding at least one salt to the aqueous solution to form a salt solution; and

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow sufficient additional oligonucleotides to bind to the nanoparticles to produce the stable nanoparticle-oligonucleotide conjugates.

524. (New) The method of Claim 523 wherein the oligonucleotides and nanoparticles are contacted in aqueous solution for about 12 to about 24 hours.

525. (New) The method of Claim 523 wherein salt is added to the aqueous solution to form the aqueous salt solution that is buffered at pH 7.0 and that contains about 0.1 M NaCl.

526. (New) The method of Claim 523 wherein the oligonucleotides and nanoparticles are contacted in the salt solution for an additional 40 hours to increase the density of oligonucleotides bound to the nanoparticles.

527. (New) The method of Claim 523 wherein the salt is added to the aqueous solution in a single addition.

528. (New) The method of Claim 523 wherein the salt is added gradually to the aqueous solution over time.

529. (New) The method of Claim 523 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

530. (New) The method of Claim 523 wherein the salt is sodium chloride in a phosphate buffer.

531. (New) The method of Claim 523 wherein nanoparticle-oligonucleotide conjugates are produced having the oligonucleotides present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

532. (New) The method of Claim 531 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

533. (New) The method of Claim 532 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

534. (New) A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides having covalently bound thereto a moiety comprising a functional group which can bind to the nanoparticles, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles in aqueous solution for a period of time sufficient to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles;

adding at least one salt to the aqueous solution to form a salt solution; and
contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow additional oligonucleotides of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

535. (New) The method of Claim 534 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

536. (New) The method of Claim 535 wherein the nanoparticles are gold nanoparticles.

537. (New) The method of Claim 536 wherein the moiety comprising a functional group which can bind to the nanoparticles is an alkanethiol.

538. (New) The method of Claim 534 wherein the oligonucleotides are bound to the nanoparticles through sulfur linkages.

539. (New) The method of Claim 534 wherein the oligonucleotides and nanoparticles are contacted in aqueous solution for about 12 to about 24 hours.

540. (New) The method of Claim 534 wherein salt is added to the aqueous solution to form the aqueous salt solution that is buffered at pH 7.0 and that contains about 0.1 M NaCl.

541. (New) The method of Claim 534 wherein the oligonucleotides and nanoparticles are contacted in the salt solution for an additional 40 hours to increase the density of oligonucleotides bound to the nanoparticles.

542. (New) The method of Claim 534 wherein the salt is added to the aqueous solution in a single addition.

543. (New) The method of Claim 534 wherein the salt is added gradually to the aqueous solution over time.

544. (New) The method of Claim 534 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

545. (New) The method of Claim 534 wherein the salt is sodium chloride in a phosphate buffer.

546. (New) The method of Claim 534 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm².

547. (New) The method of Claim 546 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm².

548. (New) The method of Claim 547 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm² to about 40 picomoles/cm².

549. (New) The method of Claim 534 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion having attached to it the moiety comprising a functional group which can bind to the nanoparticles.

550. (New) The method of Claim 549 wherein the spacer portion comprises at least about 10 nucleotides.

551. (New) The method of Claim 550 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

552. (New) The method of Claim 549 wherein the bases of the nucleotides of the spacers are all adenines, all thymines, all cytosines, all uracils, or all guanines.

553. (New) The method of Claim 549 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

554. (New) The method of Claim 553 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

555. (New) The method of Claim 534 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

556. (New) The method according to any one of claims 433, 500, 523, or 534 wherein the salt solution has an ionic strength sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other.